## II. RESPONSE TO OFFICE ACTION

### A. Status of the Claims

Claims 6, 8-9 and 14-23 are pending. Claims 6, 8, 14, 16-10 have been amended. Support for the amendments can be found in various places throughout the specification, including but not limited to the second paragraph of the summary and first paragraph of the detailed description.

### B. Section 112, First Paragraph Rejections

The Action first rejects claim 6 and 16-20 under 35 USC 112, first paragraph, with the Action taking the position that while the specification is enabling for a method for measuring the amount of oxidative stress by detecting the amount of DNA damage, it does not reasonably provide enablement for detecting mtDNA damage by measuring mt mRNA production, mt protein production, mt oxidative phosphorylation, mt ATP production or changes in oxidative redox state.

In response, Applicants submit that the Action again fails to set forth any cognizable evidence to support its position of non-enablement and, as such, has failed to set forth a *prima facie* case based on substantial evidence as the law requires. *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). To make out a *prima facie* rejection, an examiner is required to come forward with evidence or sufficient reasoning substantiating the doubts advanced. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974). The Examiner has attempted to address this issue merely by what appears to be facts within the examiner's own personal knowledge, which facts have not

been substantiated on this record as required by 37 C.F.R. 1.104(d)(2). Thus, if the Examiner persists in this rejection, and continues to rely on the personal knowledge discussed below, she is required to submit an affidavit setting forth this knowledge with particularity.

Before turning to the specifics of the rejection, Applicants first point out that the real "enablement" question here is whether one of skill in the art can carry out the assay as claimed – *i.e.*, whether one of skill in the could undertake a measurement of mt mRNA production, for example. Yet, there has been no suggestion in the Action that one of skill in the art would not be enabled to carry out such an assay, merely whether such an assay would be reasonably predictive of mtDNA damage. Thus, the question is perhaps more appropriately considered one of operability/utility.

***The Action Fails to Set Forth Evidence of Unpredictability***

Turning to the Action's comments, in an attempt to satisfy the *Wands* criteria, the Action first takes the position that that the relationship between mitochondrial ("mt") DNA damage is not quantitatively related to mt mRNA production, mt protein production, mt oxidative phosphorylation, mt ATP production or changes in oxidative redox state, and yet provides no support for this conclusion. Rather, the Action simply states that the "art teaches that tissue ischemia, OXPHOS gene defects, environmental toxins, mtDNA mutations, decreased cellular ATP and oxygen radical formation all affect phosphorylation dysfunction which leads to tissue degeneration and cell death" referring to the article of Corral-Debrinski *et al.*, 1992. Action at page 3. The Action then states that "[t]he art does not teach how the amount of mtDNA damage is affected or associated by each of these factors.

Applicant again observes that the statement lifted by the Examiner from the Corral-Debrinki *et al.* article in no way supports a conclusion of non-enablement. Rather, it serves the opposite purpose and indeed supports enablement: Corral-Debrinki *et al.* itself states "[t]his cumulative mtDNA damage was associated with a compensatory 3.5-fold induction of nuclear OXPHOS gene mRNA" and goes on to report a correlation between oxidative stress and elevated mitochondrial damage.[1] So, the Examiner has failed to set forth any cognizable teaching to support her position of non-enablement. Thus, the only "evidence" of non-enablement appears to be facts within the Examiner's own personal knowledge, which facts have not been substantiated on this record as required by 37 C.F.R. 1.104(d)(2).

Further, in Applicant's previous response various pieces of scientific literature were presented to rebut the Examiner's statement that the art fails to show a correlation between DNA damage and the aforementioned factors. These references included Ballinger *et al.*, Cadenas *et al.* and Halmosi *et al.* In the present Action, while the Examiner appears to concede that these references demonstrate the necessary correlation, it was indicated that since the references were published after the priority date, they could not be considered as evidence of enablement. Accordingly, Applicant's present additional references, each published just prior to Applicant's priority date.

First, Applicant directs the Examiner's attention to the Lenaz article (*Biochimica et Biophysica Acta* 1366, 1998, pp 53-67; copy enclosed). In its abstract, Lenaz references the "vicious cycle" established between mtDNA damage and altered oxidative phosphorylation and overproduction of reactive oxygen species. The article of Hudson *et al.* (*Free Rad. Res.*, vol 29,

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[1] Of course, a principal advance of the presently claimed invention over Corral-Debrinski *et al.* is that the present claims are directed to measuring such damage in tissues other than heart tissues, which would be an impractical screen for the population as a whole.

pp. 573-579, 1998; copy enclosed) references the contribution of mtDNA damage to a decrease in mitochondrial cytochrome c oxidase (COX) activity, associated with a reduction in COX gene and protein expression and a similar decrease in the rate of mitochondrial protein synthesis. See first paragraph, page 573. Lastly, attention is directed to the article of Williams *et al.* (of record as reference C48), which demonstrates that "altered mitochondrial function" is correlated with increased oxidative damage (by virtue of incorporating 8-hydroxydeoxygunosine into DNA), including "oxygen consumption" and "ATP production." See, *e.g.*, title, first full paragraph, page 28510 and last paragraph, page 28515.

***Guidance in the Specification – Working Examples***

The Action next points out the support in the specification for the subject matter of the rejected claims, and concludes that there is insufficient exemplary support to demonstrate that the claimed invention is operable with respect to the various alternative "indirect" methods for measuring mt DNA damage. We submit that the presence or absence of working examples is ordinarily an insufficient basis for finding non-enablement. *Ex parte Nardi*, 229 USPQ 79 (BPAI 1986). This is particularly true where, as here, the question is not whether one of skill can appropriately carry out the assay, it is really whether the assay is reasonably predictive of mtDNA damage.

In an attempt to support a conclusion of non-operability, the Action states at the top of page 5, that an mtDNA mutation could lead to a protein production of zero and that this would, according to the Examiner, not provide any guidance as to the quantity of DNA damage.

We would respond to this by observing that the examiner's scientific reasoning, which is unsupported by any affidavit or art, is totally unfounded and contrary to what a scientist would

expect, which is that the ultimate expression of a particular mt gene would very definitely be directly related to the amount of random damage in that particular gene. For example, let's say we have a population of 100 mitochondria, each having one gene coding for "X". If 20 of the 100 mitochondria have mutational "hits" in them, one would very definitely expect there to be about a 20% reduced activity of the gene product as compared to a 100 mitochondria control with no such mutational hits. The Examiner's scientific reasoning is very definitely faulty in that she tries to look at a single gene of a single mitochondria rather than a population of mitochondria, which is what is going to be measured in a blood sample!

Next, the Examiner argues, again without any scientific support or affidavit, that some lesions or mutations may occur in non-coding regions and thus would not affect protein production. This analysis, while perhaps applicable to a situation where one is looking at a single mitochondria, again misses the point for essentially the same reason. Where there is a *population* of mitochodria being tested (which there certainly would be if one were testing a blood sample or blood products as stated by the claim), there would necessarily be a vast range of mutations occurring in the mitochondria, some within coding regions and some outside of a particular coding region. Nevertheless, the distribution would be expected to be random and thus demonstrate a readily identifiable *correlation* between the amount of damage in any one gene, as measured by expression of that gene, and the amount of damage overall. The Examiner in fact confirms this by correctly stating that the "knockout of mitochondrial enzyme with a single mutation could cause dysfunction." That's precisely the point: in any population of mitochondria there will be a distribution of gene knockouts by mutation and the level of that distribution of knockouts, as reflected by the activity or amount of the particular mt protein or mRNA being measured will reflect the degree of DNA damage. If *every single* mitochondria in

the sample has that particular mt protein or mRNA knocked out – whether that protein or mRNA is involved in ATP production or mitochondrial redox state – you darn well know that *that* patient has some real problems with their mitochondria!

Lastly, responding to the Examiner's allegation that the specification does not teach a direct tie between mt gene mutations and the activity of mt gene products, we would state that a direct tie between the amount of gene mutational damage and the expression of *any* given gene, mRNA, *etc.*, is, simply put, self evident, and the Examiner has presented no evidence to the contrary.

***Quantity of Experimentation***

Turning to the next section of the non-enablement rejection, that dealing with quantity of experimentation, the Examiner again fails to come forth with any cognizable evidence and merely states, incorrectly, in a conclusory fashion that there "are many other factors which would affect each of these quantities which may not be related to the amount of mtDNA damage." However, the Examiner notably fails to point to any such "many other factor" in either any scientific literature or in an affidavit as required by 37 CFR §1.104(d)(2).

Thus, as explained above, the Action fails to set forth a *prima facie* case of inoperability of the rejected claims.

## C. Section 112, Second Paragraph Rejections

The Action next rejects claims 6, 8-9 and 14-23, stating that the claims are indefinite in that it is said to be unclear whether the method of claim 6 is directed to "detecting amount" or "mere presence." In response, it is now clear from amended claim 6 that said claim is directed to

"assessing the amount" of damage. It is believed that this amendment adequately addresses the Examiner's concerns.

**D. Section 102 Rejections**

The Action next rejects claims 6 as anticipated by Filser *et al.* Applicants respectfully traverse.

In response, it is noted that Filser *et al.* is totally irrelevant to, and teaches away from, the successful use of "hematopoietic" tissues. Filser *et al.* teaches the use of a particular assay which measures a particular deletion in mtDNA. Yet, in the context of "heart, lung, muscle, and bone marrow the deletion could not be *quantified* because of a point mutation". Abstract, page 102 (emphasis ours). Thus, in the context of hematopoietic tissues such as bone marrow, Filser *et al.* actually evidence of failure and thus teaches away from the obviousness of the claimed invention.

Additionally, the claims are now directed to using blood samples from human patients. Filser *et al.* is thus even further removed from the claimed invention, as it fails to in any way teach or suggest a blood sample from a human.

**E. Section 103 Rejections**

Lastly, the Action enters various obviousness rejections of various of the claims over Yan *et al.* in view of Filser *et al.* (claims 6, 7, 8, 9, 14, 15, 21) and further in view of VenMurthy *et al.* (claim 23) or Van Houton (claim 22).

Since the claims are now directed to testing blood samples, Applicants will focus their argument on the claim 23 rejection.

We respectfully traverse and contend that the Examiner has failed to set forth a proper *prima facie* case of obviousness as there is clearly no motivation to combine these references. As noted by the Action, Yan *et al.* made an observation based on the mitochondria of diseased *aortic atherosclerotic* tissue as compared to normal aortic tissue. However, while VenMurthy makes reference to testing lymphocytes, *those* assays clearly failed to demonstrate *any* difference in the mtDNA mutations of positive versus negative control samples. Thus, since VenMurthy admittedly failed to demonstrate any difference it can in no way be said that the skilled artisan would seek to combine this reference with any reference, much less one like Yan *et al.* dealing with aortic tissue. Stated another way, there was clearly no expectation that were Yan to test the lymphocytes of VenMurthy that such a test would be successful – indeed, the very VenMurthy reference itself suggests that such a test would *not* be successful!

The Examiner's inclusion of Filser *et al.* in odd in that, for the reasons discussed above, Filser *et al.* actually supports a conclusion of non-obviousness in the Filser *et al.* teaches that the mtDNA could not be quantified in hematopoietic tissues (in particular, bone marrow). See 7$^{th}$ sentence of Abstract.

The Examiner is therefore earnestly requested to reconsider and withdraw the pending obviousness rejections, and pass the case to allowance.

## CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner and the undersigned attorney at 512-536-3055 is respectfully requested.

Respectfully submitted,

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